International Journal of Research in Medical Sciences
Kermawan P et al. Int J Res Med Sci. 2024 Aug;12(8):3063-3068
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20241958

Review Article

The pharmacological effects of glucosamine chondroitin, chitosan, and phytoestrogen on knee osteoarthritis

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Received: 04 June 2024
Revised: 04 July 2024
Accepted: 05 July 2024

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ABSTRACT

Osteoarthritis (OA) of the knee significantly disrupts daily activities and reduces quality of life due to pain. The primary treatment involves anti-inflammatories, which can cause stomach issues. Alternative therapies, including glucosamine, chondroitin, chitosan, and phytoestrogens, are being explored, but their effects need further study. While some benefits may be due to the placebo effect, researchers conducted a literature review to determine their actual benefits. A review of seven meta-analyses found that glucosamine and chondroitin can alleviate pain, reduce stiffness, improve function, and reduce joint space narrowing (JSN) in OA patients. Chitosan's use in intra-articular injections for OA has been studied in four observational studies and clinical trials on animals, but the effects of oral chitosan supplements remain unknown. A literature review on phytoestrogens in OA, particularly in post-menopausal women, identified four relevant studies. The review suggests that glucosamine, chondroitin, chitosan, and phytoestrogens have significant therapeutic benefits for OA, such as reducing pain (measured by VAS score), relieving stiffness, and improving functionality due to their anti-inflammatory and chondroprotective effects. Therefore, additional randomized controlled trials are needed to confirm their effectiveness in managing knee OA.

Keywords: Knee OA, Glucosamine chondroitin, Chitosan, Phytoestrogens

INTRODUCTION

Osteoarthritis (OA) of the knee is an inflammatory condition that significantly disrupts daily activities due to the pain it causes, ultimately reducing the sufferer's quality of life. The primary treatment for knee osteoarthritis currently involves the use of anti-inflammatories, which can have side effects on the stomach. To avoid these side effects, many alternative therapies have been explored, including treatments containing glucosamine, chondroitin, chitosan, and phytoestrogens, though their effects require further study. OA is a progressive disease that can lead to disability. Clinical symptoms vary among individuals, but the disease typically becomes more severe, frequent, and debilitating over time. Common symptoms include gradually worsening knee pain with activity, knee stiffness and swelling, pain after sitting or resting for a long period, and progressively worsening pain.[1,2]

Osteoarthritis of the knee is an inflammatory condition that significantly disrupts daily activities due to the pain it causes. The burden of musculoskeletal disease has risen substantially, making it the second leading cause of years lived with disability (YLD).[3] In 2015, back and neck pain were the primary contributors to YLD among musculoskeletal disorders, with OA following closely, accounting for approximately 7.1% of this burden and

showing a statistically significant increase. Between 1990 and 2007, there was a 63.1% increase in OA cases. Treatment for knee OA typically starts with conservative methods and progresses to surgical options when conservative treatments fail. While medications can help slow OA progression and manage other inflammatory conditions, there are currently no disease-modifying agents proven to completely treat knee OA. The primary therapy involves using anti-inflammatories, which can have side effects on the stomach.[4,5]

The anti-inflammatory therapy often given for knee OA is ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID). However, prolonged or high-dose use of ibuprofen can cause ulceration in the stomach or intestines. Additionally, intra-articular corticosteroid injections can be effective for symptomatic knee OA, particularly when there is significant inflammation. These injections reduce local inflammation with fewer systemic steroid effects, though patients generally prefer oral medications over injections.[6-8]

To mitigate the gastrointestinal side effects of NSAIDs, gastroprotective agents are often used. A survey study found that the most commonly prescribed gastroprotective agents are proton pump inhibitors (PPI) (94.61%) and H2 antagonists (5.38%) Additionally, paracetamol can be used to treat OA as it has no gastrointestinal side effects, although it is less effective than ibuprofen.[8-10]

Glucosamine, chondroitin sulfate, chitosan, and phytoestrogen supplements are often used as alternative treatments to avoid the side effects of NSAIDs, although their efficacy requires further study. Glucosamine and chondroitin sulfate, available as dietary supplements, are structural components of articular cartilage and may support cartilage health. While there is no strong evidence supporting their benefits in treating knee OA, they are relatively safe with no significant toxicity. Patients informed about the studies behind these supplements and willing to take them may find them a safe therapy option. The perceived benefits from glucosamine, chondroitin sulfate, chitosan, and phytoestrogen supplementation are likely due to the placebo effect. Therefore, researchers aim to conduct a literature review to determine the benefits of glucosamine, chondroitin, chitosan, and phytoestrogens in OA treatment.[11-13]

GLUCOSAMINE CHONDROITIN

Since glucosamine and chondroitin are components of cartilage, it has been proposed that they might influence joint structure in OA, potentially measurable through changes in joint space. However, it remains uncertain whether glucosamine and chondroitin truly affect joint structure. Researchers conducted a review of meta-analysis to examine the effects of glucosamine and chondroitin on alleviating pain, reducing stiffness, improving function, and reducing JSN in patients with OA. Seven meta-analyses reported benefits of glucosamine and chondroitin.[14]

A meta-analysis by Zhu et al included twenty-six articles of clinical trials found that chondroitin could alleviate pain symptoms and improve function compared to placebo. Glucosamine showed a significant effect only on stiffness improvement when compared to placebo. However, there was not enough evidence to suggest that the combination therapy of glucosamine and chondroitin was superior to placebo.[15]

A meta-analysis by Mendia et al found that treatments with glucosamine and chondroitin significantly reduced pain on the visual analogue scale (VAS) [weighted mean difference (WMD)-7.41 mm, 95% CI-14.31 to -0.51, p=0.04 for glucosamine, and WMD -8.35 mm, 95% CI -11.84 to -4.85, p<0.00001 for chondroitin]. Additionally, neither glucosamine, chondroitin, nor their combination had a significant positive effect on the total WOMAC index and its subscores.[14]

A meta-analysis by Meng et al included eight randomized controlled trials (RCTs) with a total of 3,793 patients, the result for the total WOMAC score, the combination group showed a statistically significant advantage compared to the placebo group [MD=-12.04 (-22.33 to -1.75); p=0.02], while the other groups showed no significant difference. Regarding the VAS score, none of the comparisons showed significant differences. In the secondary outcomes, the only significant differences were observed in the comparison of JSN between the combination and placebo groups [MD=-0.09 (-0.18 to-0.00); p=0.04].[6]

The review by Ogata et al analyzed recent randomized controlled trials on glucosamine for knee OA. Eighteen articles written between 2003 and 2016 were included. Many studies used VAS pain scores and the Western Ontario and McMaster universities OA index (WOMAC), both of which were assessed in the meta-analysis. The analysis found a marginally favorable effect of glucosamine on VAS pain scores, but the effect on knee function measured by the WOMAC was small and not significant.[7,16]

A meta-analysis by Zeng et al included a total of 54 studies covering 16,427 patients. The analysis found that glucosamine plus chondroitin, and glucosamine alone were all more effective than placebo for pain relief and function improvement. Regarding the structure-modifying effect, both glucosamine alone and chondroitin alone achieved a statistically significant reduction in JSN.[16,17]

Study by Rabade et al analyzed 25 randomized controlled trials (RCTs) using meta-analysis. Results indicated that chondroitin sulfate (CS) significantly reduced pain intensity and improved physical function compared to placebo. Glucosamine sulfate (GS) significantly reduced tibiofemoral JSN. However, the combination of GS and

CS showed neither a reduction in pain intensity nor any improvement in physical function and JSN.[11]

A study by Singh et al which included forty-three randomized controlled trials with 9,110 participants, found that participants treated with chondroitin achieved statistically significant and clinically meaningful better pain scores in studies lasting less than 6 months. The loss of minimum joint space width in the chondroitin group was statistically significantly less than in placebo group. Chondroitin, whether taken alone or in combination with glucosamine, showed a statistically significant reduction in pain (0-100) when compared with placebo. However, for physical function, chondroitin in combination with glucosamine showed no statistically significant difference from placebo.[13]

The Table 1 below summarizes the findings regarding the effects of glucosamine and chondroitin on various outcomes in patients with OA, as reported in different meta-analyses and studies.

Table 1: Effects of glucosamine and chondroitin on various outcomes in patients with OA, as reported in different meta-analyses and studies.

Authors (year)	Pain relief	Stiffness education	Function improvement	WOMAC index	JSN
Zhu et al (2018)[15]	Significant (C)	Significant (C)	Significant (C)		
Mendia et al (2018)[14]	Significant (G)(C)				
Meng et al (2023)[6]				Significant (GC)	Significant (GC)
Ogata et al (2018)[7]	Significant (G)				
Zeng et al (2015)[16]	Significant (G)(GC)		Significant (G)(GC)		Significant (G)(C)
Rabade et al (2024)[11]	Significant (C)		Significant (C)		
Singh et al (2015)[13]	Significant (C)(GC)				

(G): intervention with glucosamine alone, (C): intervention with chondroitin alone and (GC): intervention with glucosamine plus chondroitin

This review revealed that glucosamine and chondroitin have some significant therapeutic benefits. Hence, there is a need for conducting more randomized controlled trials to evaluate and confirm the therapeutic role of the glucosamine and chondroitin combination in the management of knee OA.

CHITOSAN

Chitosan is a linear polysaccharide derived from the deacetylation of chitin, the primary structural polymer found in exoskeleton of marine invertebrates, insects, and cell walls of fungi. Cs has been proven to be chondroprotective and to increase chondrocyte proliferation when injected intra-articularly in rat and rabbit OA models.[12]

There is still limited research discussing the effects of chitosan, both injected and orally, on OA. The latest method of using chitosan for intra-articular injection has been widely explored in observational studies and clinical trials on test animals. However, the effect of using oral chitosan supplements for OA remains undiscovered. The following are the results of a review of 4 observational study on the use of chitosan injections:

An observational study on humans by Lynen et al involved 49 knee OA patients who received a single injection of 60 mg CM-chitosan. The study showed that the VAS pain score significantly decreased from a median of 49.0 mm at baseline to 24.0 mm at week 1, and further to 18.0 mm at week 36. All KOOS subscales (symptoms, pain, activities of daily living, sports and recreational activities, quality of life) showed significant improvement compared to baseline at all time points. Specifically, KOOS pain scores improved progressively from a median of 58.3% at baseline to 86.1% at week 36. Overall, more than 70% of patients reported a condition gain (PGA), which corresponded with over 75% of patients being satisfied with the treatment.[10]

An observational study on humans by Emans et al involved patients with painful knee OA who were randomly assigned to receive either a CM-chitosan intra-articular injection (n=63) or Durolane® as a control (n=32). Patients were blinded to the treatment and followed up for 26 weeks. The primary objective was met, showing a mean pain reduction of 62.5% (effect size 2.08) for the KiOmedine® CM-chitosan group and 62.4% (effect size 2.28) for the Durolane® group.[18]

An observational study on rabbits by Rieger et al involved 18 rabbits that underwent unilateral anterior cruciate ligament transection (ACLT) to induce OA. The study compared the effects of a hybrid injection (chitosan and hyaluronic acid) to hyaluronic acid (HA) alone. The results showed that the hybrid-group significantly improved subchondral bone microarchitectural

parameters, including subchondral plate thickness and trabecular thickness, as well as trabecular bone mineral densities (bone mineral density and tissue mineral density), compared to HA-group.[12]

In an observational study on rats by Miao et al an injectable and self-healing hydrogel was synthesized by *in situ* crosslinking of N-carboxyethyl chitosan (N-chitosan), adipic acid dihydrazide (ADH), and hyaluronic acid-aldehyde (HA-ALD). This supramolecular hydrogel demonstrated good biocompatibility with chondrocytes. Intra-articular injection of this novel hydrogel significantly alleviated local inflammatory microenvironment in knee joints by inhibiting inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17 in the synovial fluid and cartilage at 2 and 12 weeks post-injection. Histological and behavioral tests indicated that hydrogel injection protected against cartilage destruction and relieved pain in OA rats, compared to HA injection alone.[19]

Table 2 below summarizes findings regarding effects of the chitosan injection on various outcomes in patients and the animals with OA, as reported in different studies.

Table 2: Effects of chitosan injection on various outcomes in patients with OA, as reported in different meta-analyses and studies.

Authors (year)	Research population	Intervention	Outcomes
Lynen et al (2024)[10]	49 knee OA patients	Single intra-articular injection of 60 mg CM-chitosan	VAS pain score significantly decreased All KOOS score improvement PGA improvement
Emans et al (2022)[18]	63 knee OA patients	CM-chitosan intra-articular injection	Pain decreases significantly
Rieger et al (2017)[12]	18 rabbits induced OA	Hybrid intra-articular injection (chitosan and hyaluronic acid)	Significantly improved subchondral bone microarchitectural
Miao et al (2012)[19]	rats induced OA	Intra-articular injection of hydrogel (N-chitosan + ADH + HA-ALD).	Inhibiting inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17 in the synovial fluid and cartilage Protected against cartilage destruction Relieved pain

This review highlights the promising potential of chitosan injections in managing OA symptoms, particularly in reducing pain and improving overall knee function. However, more extensive research is needed to confirm these findings and to explore the potential benefits of oral chitosan supplements for OA.

PHYTOESTROGEN

Phytoestrogens are diphenolic compounds with structural similarity to estrogens, and are consequently referred to as isoflavones. They are found mainly in legumes, with soy being a major dietary source. Isoflavones have a structure similar to 17β-estradiol, which may make them useful for postmenopausal women in preventing bone loss related to estrogen deficiency.[1] Researchers conducted a literature review on the use of phytoestrogens in OA, particularly in post-menopausal women, and identified four relevant studies, including randomized controlled trials and observational studies. The studies are discussed as follows:

A randomized controlled trial by Kirkham et al involved 75 patients with knee OA, who were randomly divided into three groups: chickpea oil, piroxicam gel, or paraffin, and received treatment for 3 months. The WOMAC scores indicated a significant decrease in pain, stiffness, and difficulty in activities in the chickpea oil group compared to the piroxicam or paraffin groups ($p<0.05$). The VAS mean pain scores were 5.42 for the placebo group, 3.92 for the piroxicam group, and 3.88 for the chickpea oil group, showing a significant difference ($p<0.001$). Additionally, chickpea isoflavones may have an anti-inflammatory effect.[20,21]

An observational study by Liu et al on a rat model of induced OA investigated the effects of genistein, a phytoestrogen extracted from soybeans. The in-vitro model showed that genistein inhibits the IL-1β-induced expression of catabolic factors such as nitric oxide synthase 2 (NOS2), cyclooxygenase 2 (COX-2), and matrix metalloproteinases (MMPs). Additionally, genistein was found to stimulate Ho-1 expression, which is linked to the activation of the Nrf-2 pathway in human chondrocytes. In the rat model, genistein also slowed the progression of traumatic OA. Overall, these findings demonstrate genistein's effectiveness in reducing inflammation associated with joint disorders.[22]

An observational study by Gundogdu et al evaluated the effectiveness of daidzein (DZ), a phytoestrogen, in treating experimental knee OA in rats. The study

involved 49 Wistar albino male rats, which were randomly assigned to groups: knee OA with saline (DC), oral DZ (po DZ), intraarticular DZ (ia DZ). DZ significantly reduced the levels of TNF-α, IL-1β, and MMP-13 in serum of DC group ($p<0.001$). Additionally, serum total antioxidant status (TAS) increased in DZ-treated groups compared to DC group ($p<0.05$). Moreover, cartilage surface cracks and fibrillation were completely resolved in groups that received DZ.[4]

An observational study by Zou et al assessed the effectiveness of genistein, a major active component of phytoestrogen, in treating experimental knee OA in rats. The study found that genistein increased the content of collagen and acid glycosaminoglycan while reducing levels of TNF-α and IL-1β. Additionally, genistein promoted expression of collagen II and aggrecan in articular cartilage and decreased expression of caspase 3, thereby alleviating cartilage degradation. Overall, results demonstrated that genistein mediated inflammation and had an anti-apoptotic effect in treating OA.[17]

The Table 3 below summarizes the findings regarding the effects of phytoestrogen on various outcomes in the patients and animals with OA, as reported in the different studies

Table 3: Effects of phytoestrogen on various outcomes in patients with OA, as reported in different meta-analyses and studies.

Authors (year)	Research population	Intervention	Outcomes
Kirkham et al (2009)[21]	75 patients with knee OA	Chickpea oil topical self-administered	VAS pain score significantly decreased WOMAC score improvement
Liu et al (2019)[22]	Rat model	Genistein per-oral	Inhibits the IL-1β, NOS2, COX-2, and MMPs stimulate Ho-1 expression, Activation of the Nrf-2 pathway in human chondrocytes.
Gundogdu et al (2020)[4]	49 Wistar albino male rats	Daidzein (DZ) intra-articular and oral	Significantly reduced the levels of TNF-α, IL-1β, and MMP-13 in the serum Increase TAS Cartilage surface cracks and fibrillation were completely resolved.
Zou et al (2020)[17]	Rats induced OA	Genistein per-oral	Increased the content of collagen and acid glycosaminoglycan Reducing the levels of TNF-α and IL-1β. Promoted the expression of collagen II and aggrecan in the articular cartilage Decreased the expression of caspase 3.

These studies collectively highlight the potential of phytoestrogens, such as chickpea oil, genistein, and daidzein, in reducing inflammation and improving symptoms in OA, particularly for post-menopausal women.

CONCLUSION

The review indicates that glucosamine chondroitin, chitosan, and phytoestrogens offer significant therapeutic benefits for OA, including reducing pain measured by VAS score, relieving articular stiffness, and improving functionality through their anti-inflammatory and chondroprotective effects. Consequently, there is a pressing need for additional randomized controlled trials to validate the therapeutic role of combining glucosamine, chondroitin, chitosan, and phytoestrogens in managing knee OA. These trials would provide more concrete evidence of their efficacy and further guide clinical practice in OA treatment.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kermawan P, Yasa IWPS, Jawi IM, Suyasa IK, Karna MB. The pharmacological effects of glucosamine chondroitin, chitosan, and phytoestrogen on knee osteoarthritis. Int J Res Med Sci 2024;12:3063-8.